PPCP's, PBT's, POP's & PUBS Antibiotic Resistance

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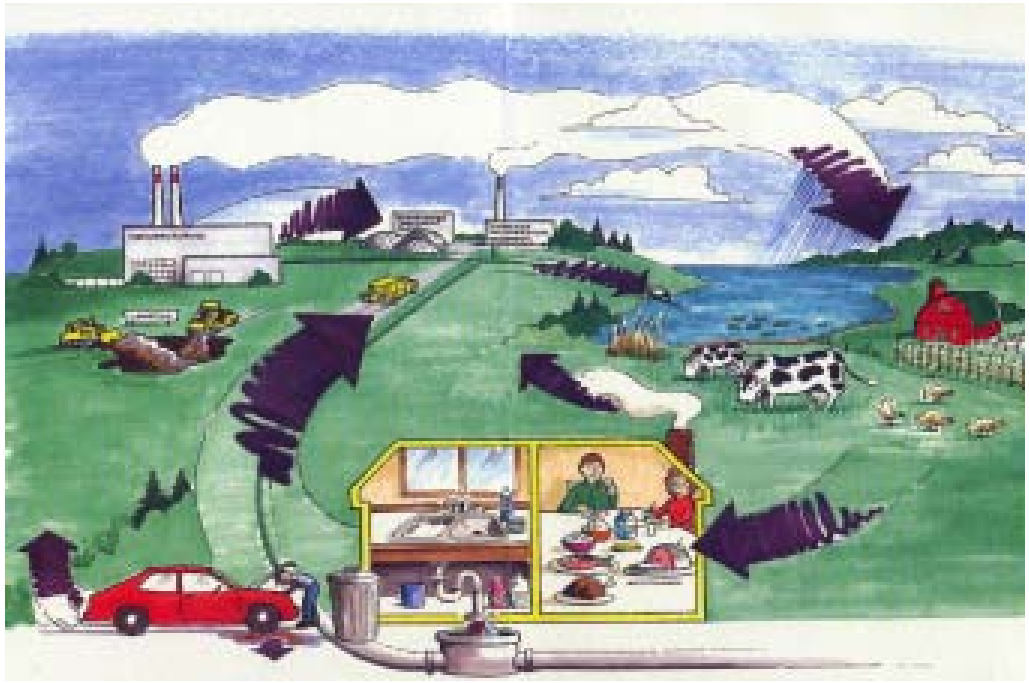
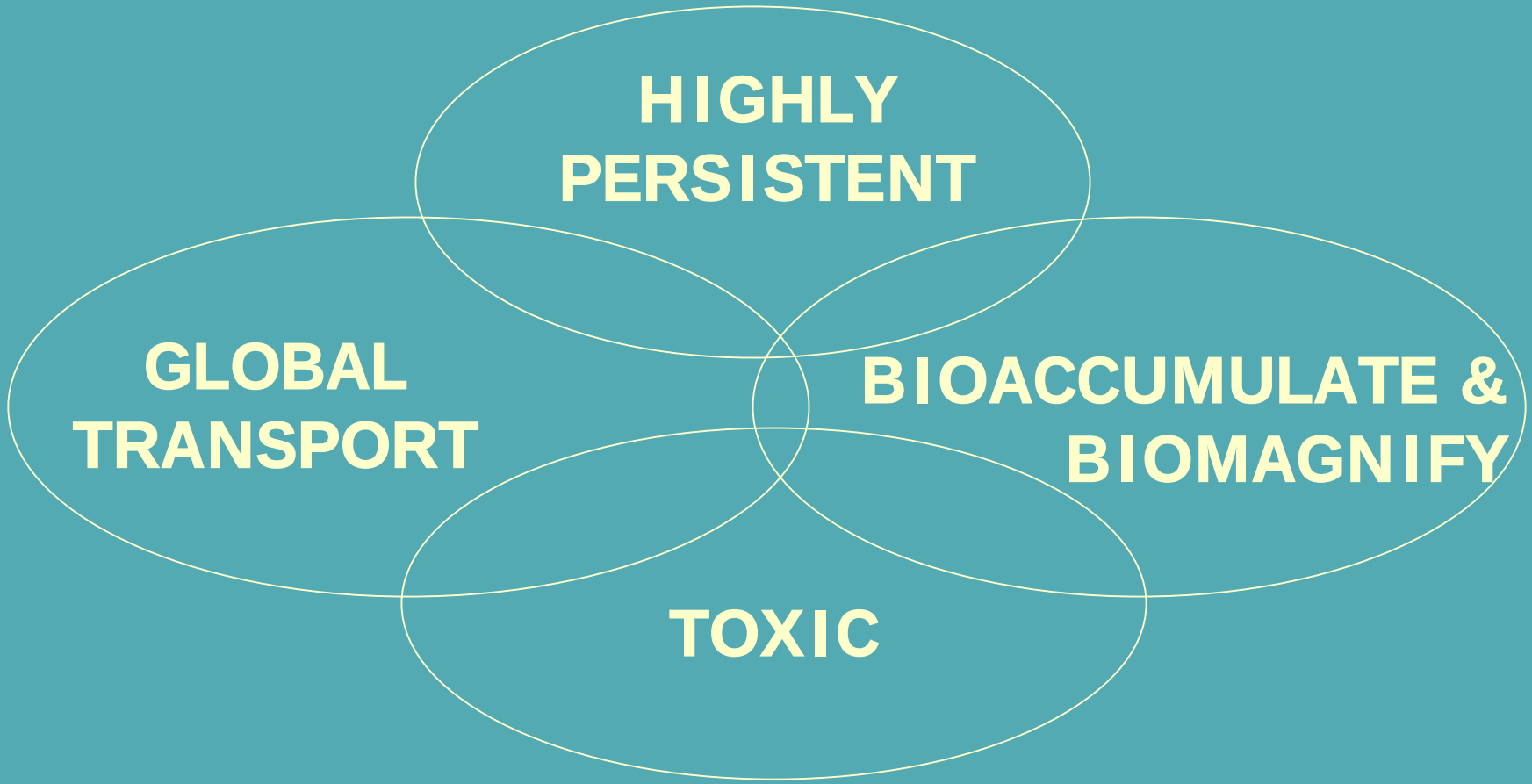
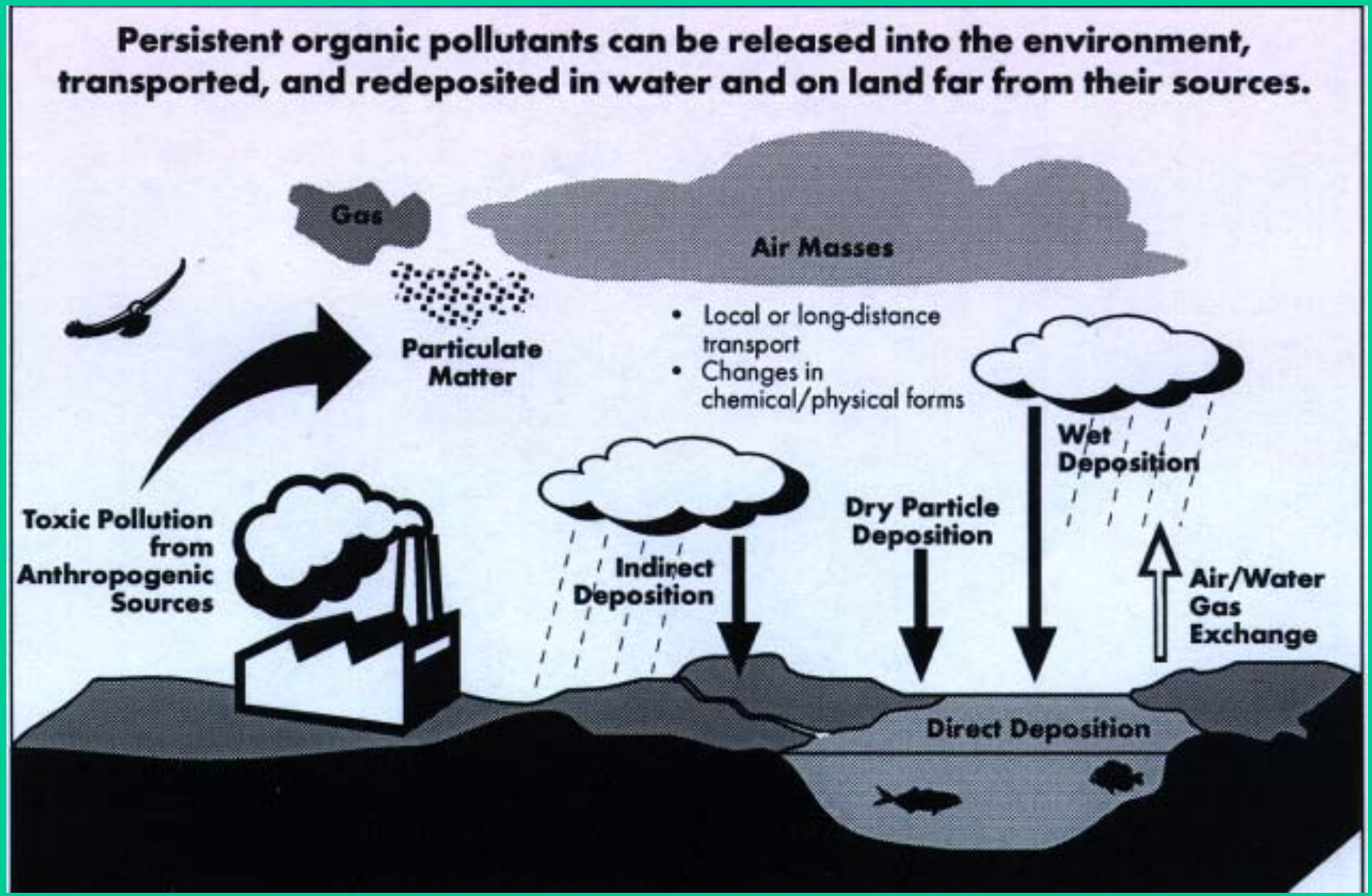
“The continued exponential growth in human population has created a corresponding increase in the demand for the Earth's limited supply of freshwater. Thus, protecting the integrity of our water resources is one of the most essential environmental issues of the 21st century. Recent decades have brought increasing concerns for potential adverse human and ecological health effects resulting from the production, use, and disposal of numerous chemicals that offer improvements in industry, agriculture, medical treatment, and even common household conveniences. ***Research has shown that many such compounds can enter the environment, disperse, and persist to a greater extent than first anticipated.*** Some compounds, such as pesticides, are intentionally released in measured applications. Others, such as industrial byproducts, are released through regulated and unregulated industrial discharges to water and air resources. Household chemicals, pharmaceuticals, and other consumables as well as biogenic hormones are released directly to the environment after passing through wastewater treatment processes (via wastewater treatment plants, or domestic septic systems), which often are not designed to remove them from the effluent. Veterinary pharmaceuticals used in animal feeding operations may be released to the environment with animal wastes through overflow or leakage from storage structures or land application. As a result, there are a wide variety of transport pathways for many different chemicals to enter and persist in environmental waters.” Abstract for ***USGS Survey: “Pharmaceuticals, Hormones, and Other Organic Wastewater Contaminants in U.S. Streams, 1999-2000: A National Reconnaissance”***

Persistent Toxic Cycle



The Unique Threat of POPs




Persistent organic pollutants can be released into the environment, transported, and redeposited in water and on land far from their sources.
Gas
Air Masses
Particulate Matter
• Local or long-distance transport
• Changes in chemical/physical forms
Wet Deposition
Toxic Pollution from Anthropogenic Sources
Indirect Deposition
Dry Particle Deposition
Air/Water Gas Exchange
Direct Deposition

How Are We Exposed To POPs?

POPs in Our Diet

Sampling reveals:

- Freshwater fish are the largest dietary source of dioxins, furans and PCBs
- Despite 1972 DDT ban, DDE levels persist in U.S. food supply

- Breast-feeding infants may be exposed more than children and adults

Source: Schecter et al (2001, 1994)

Health Effects of Various POPs

- Endocrine Disruption
- Reproductive and Developmental Harm
- Cancer
- Neurological and Behavioral Effects
- Immune toxicity and suppression
- Diabetes mellitus

What are Endocrine Disruptors?

Substances that:

- Mimic or block actions of natural hormones in body
- Interfere with synthesis, secretion, transport, binding, action, or elimination of natural hormones

Endocrine Disruption and POPs

- Many POPs are endocrine disruptors
- Endocrine disruption is linked to:
  - Reproductive and developmental harm
  - Cancer
  - Neurological and behavioral deficits
- Some of these health outcomes have increased in recent decades

“The Dirty Dozen”

Pesticides:

- Aldrin
- Endrin
- Dieldrin
- Chlordane
- DDT
- Heptachlor
- Hexachlorobenzene
- Mirex
- Toxaphene

Industrial Chemicals:

- PCBs

By-Products:

- Dioxins
- Furans

“As pharmacists and health care providers, we are trained to carefully consider all of the positive and negative effects of any pharmaceutical given to an individual patient and choose the best drug for the patient. It has ***only recently come to light that what happens to that pharmaceutical after it leaves the patient and enters the waste stream*** may be equally important to the health of our communities. For example, antibiotics in the waste stream help to increase bacterial resistance; hormones and other biologically active compounds can continue to exert their effects on humans and other living creatures; and chemotoxic agents can continue to poison cells in a variety of organisms. It's time to consider the ***full effects of the pharmaceuticals we use in humans, other animals, and agriculture*** and ***devise ways to keep these potentially dangerous substances out of the environment.” Cindy Parker, MD; PSR***

Resisting Resistance:
An Interdisciplinary Approach to Reducing Antibiotic Resistance

Prepared by Katherine M. Shea, MD, MPH

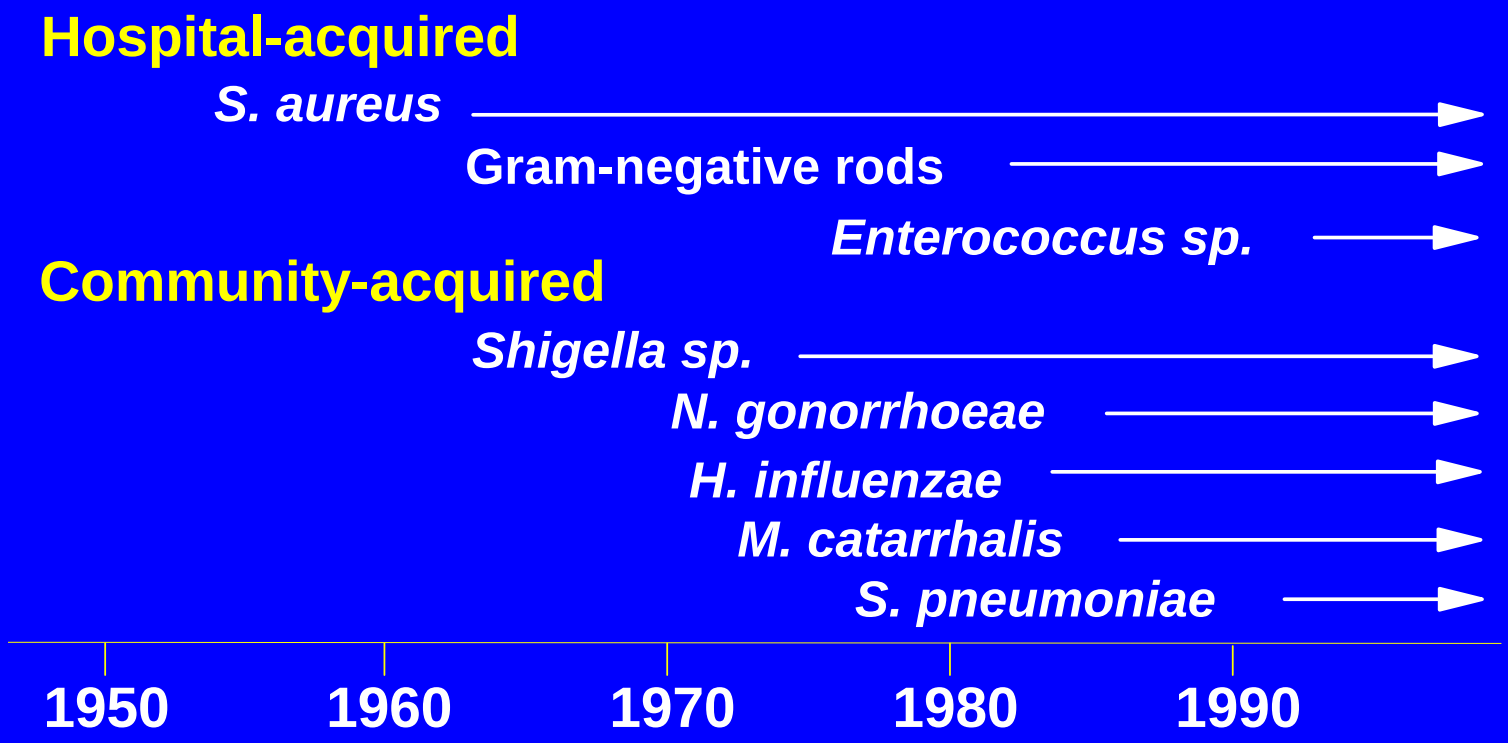
"Throughout America, infectious diseases are emerging that we may not be able to cure because bacteria have become resistant to antibiotics. For the past 60 years, the availability of antibiotic drugs has turned bacterial infections into treatable conditions, rather than the life-threatening scourges they once were. Today, however, the effectiveness of many life-saving antibiotics is waning. **Human infections from antibiotic-resistant bacteria have increased dramatically**. Everyone is at risk from antibiotic-resistant infections, but children, the elderly, and people with weakened immune systems are particularly vulnerable.

The **overuse of antibiotics** is to blame. A **major source** of this overuse is livestock producers unnecessarily **feeding antibiotics to healthy farm animals** to promote growth and compensate for unsanitary conditions. The Union Of Concerned Scientists estimates that 70% of all antibiotics in the U.S. are used in healthy pigs, poultry, and cattle. Antibiotic use in agriculture has been definitively linked to antibiotic resistance in human bacterial infections. Nonetheless, ***agribusiness and the pharmaceutical industry are fighting hard to thwart any restrictions on the use of antibiotics in agriculture***." Statement by the "Keep Antibiotics Working" campaign.

Infectious Disease Mortality in the United States, 1980-1996

Source: JAMA 1996;275:189-193 and unpublished CDC data

Emergence of Antibiotic Resistant Bacteria



Cohen;Science 1992;257:1050

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

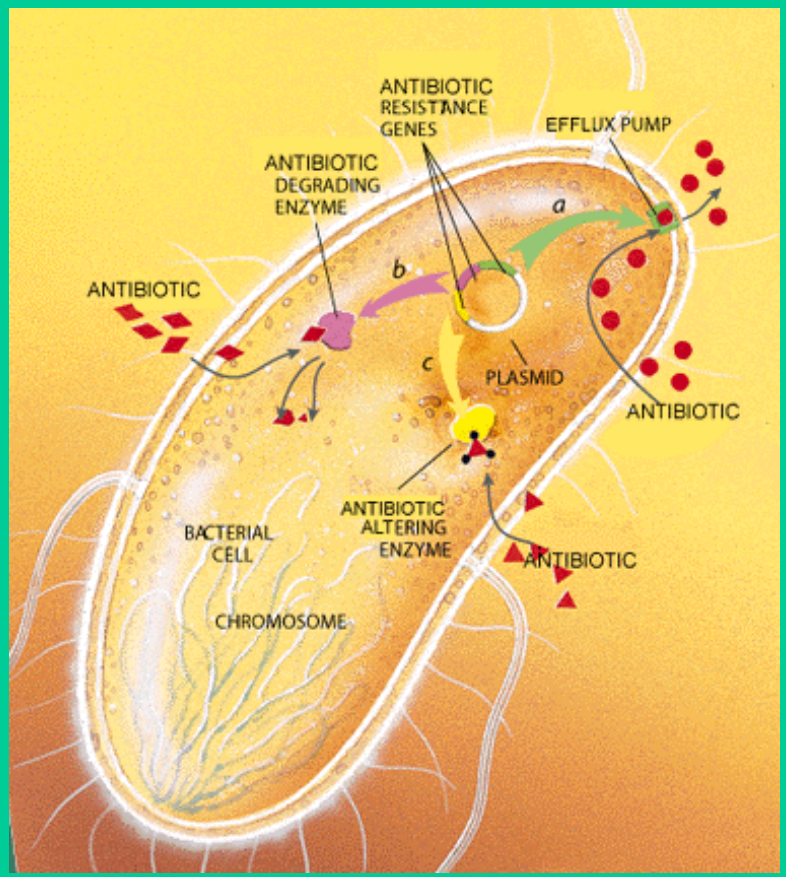
Bacteria + Antibiotic = Resistance

An Evolutionary Certainty

Antibiotic Class	Drug Discovered	Introduced-clinical use	Resistance identified
Penicillin	1940	1943	1940
Streptomycin	1944	1947	1947
Tetracycline	1948	1952	1956
Erythromycin	1952	1955	1956
Vancomycin	1956	1972	1987
Gentamicin	1963	1967	1970

Ciba. Antibiotic Resistance: Origins, Evolution, Selection and Spread, 1997

Mechanisms of Resistance

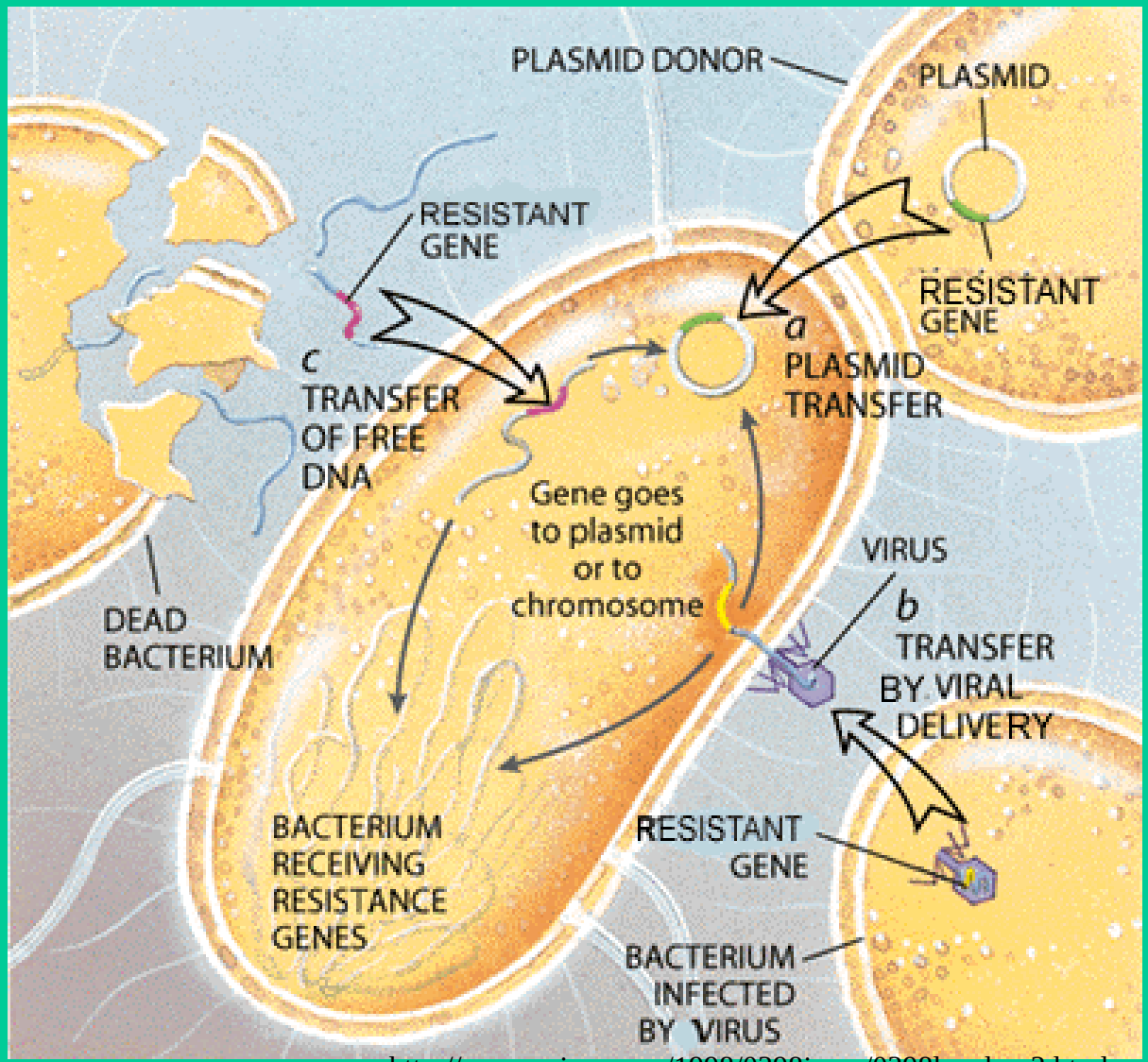


Resistance is Genetic

- Prevent Access to Site
  - Decrease Influx
  - Increase Efflux
- Inactivate Drug
- Change Site of Action

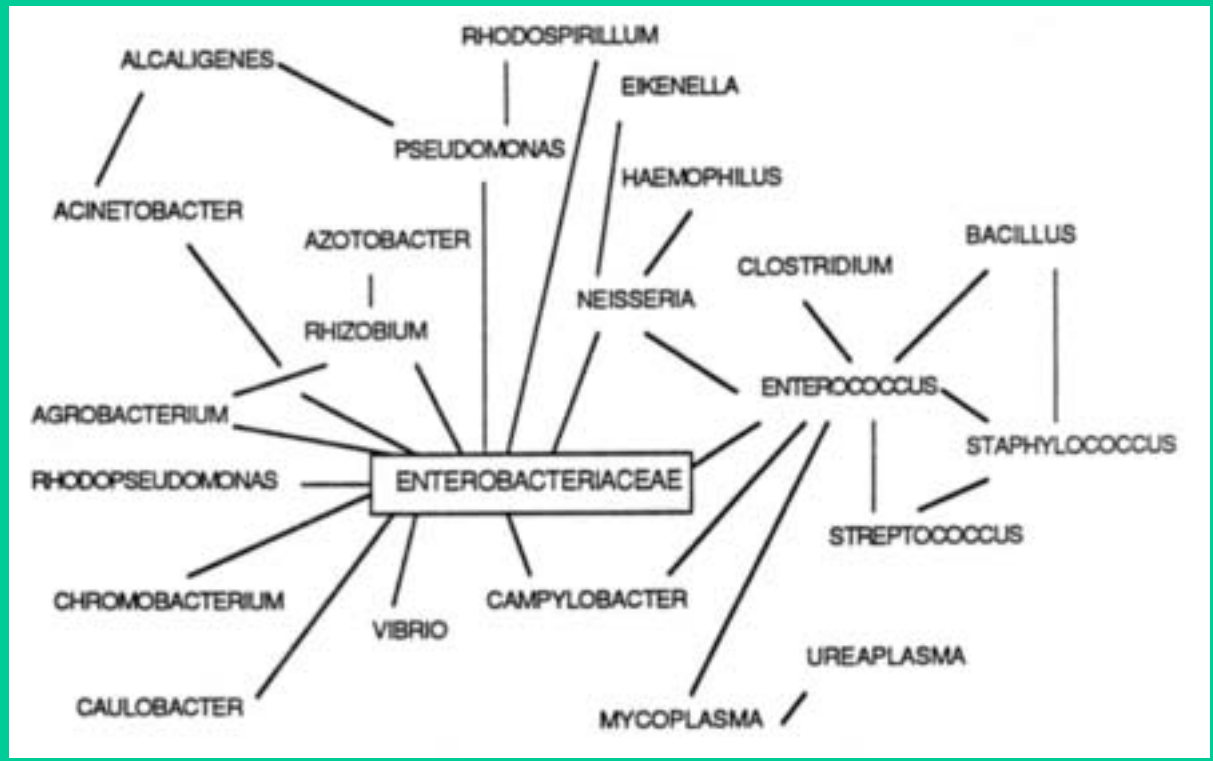
http://www.sciam.com/1998/0398issue/0398levybox2.html

Versatile Genetic Engineers



http://www.sciam.com/1998/0398issue/0398levybox3.html

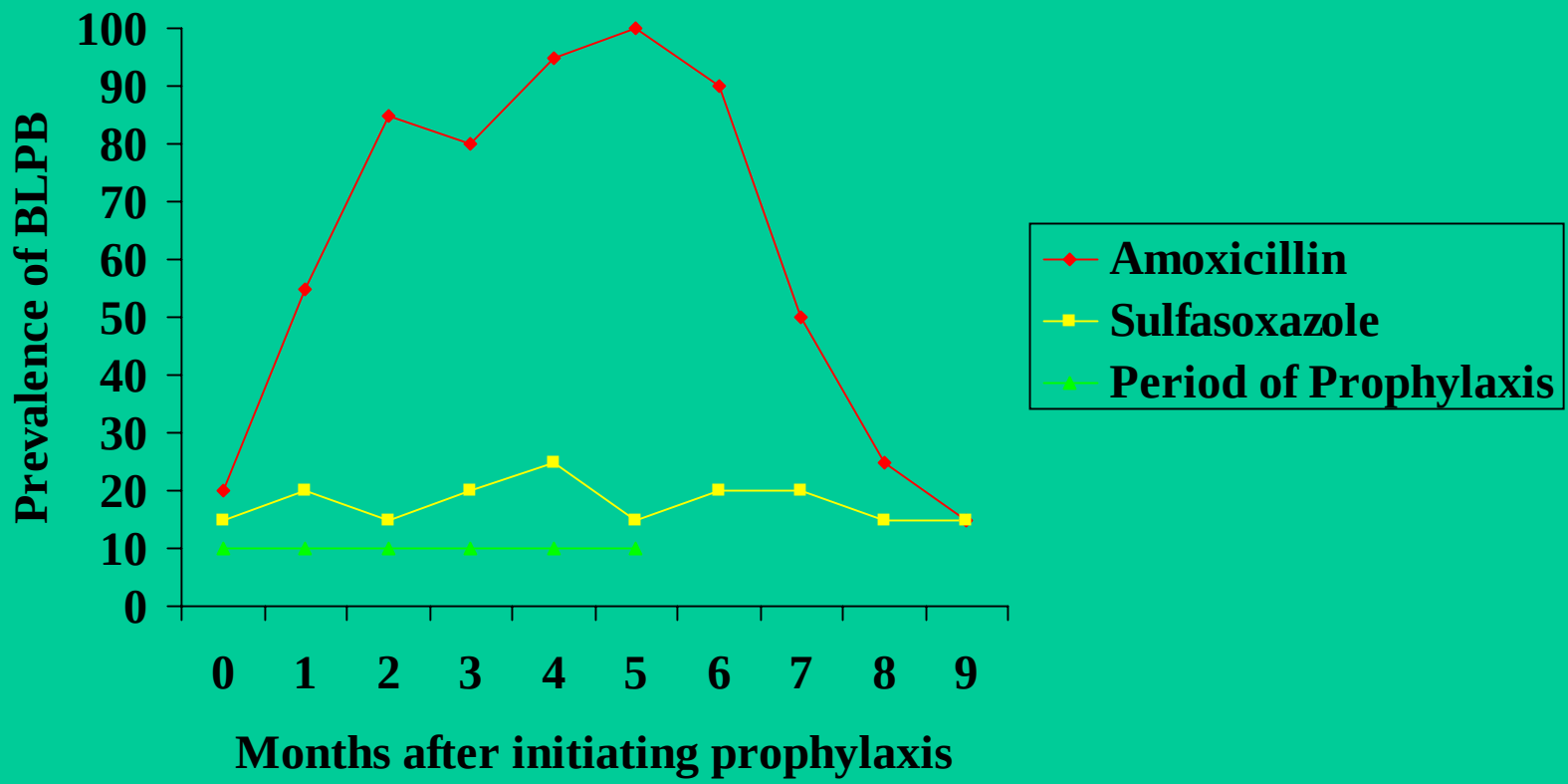
Horizontal Transmission of Resistance Genes among Species



Gene Transfer in the Environment. Levy & Miller, 1989

Bacteria + Antibiotic = Resistance

Antibiotic Exposure – Individuals



Brook Clin Infec Dis (1996) 22:143

Correlation Between Recent Antibiotic Use and Invasive Disease with Resistant S. pneumonia

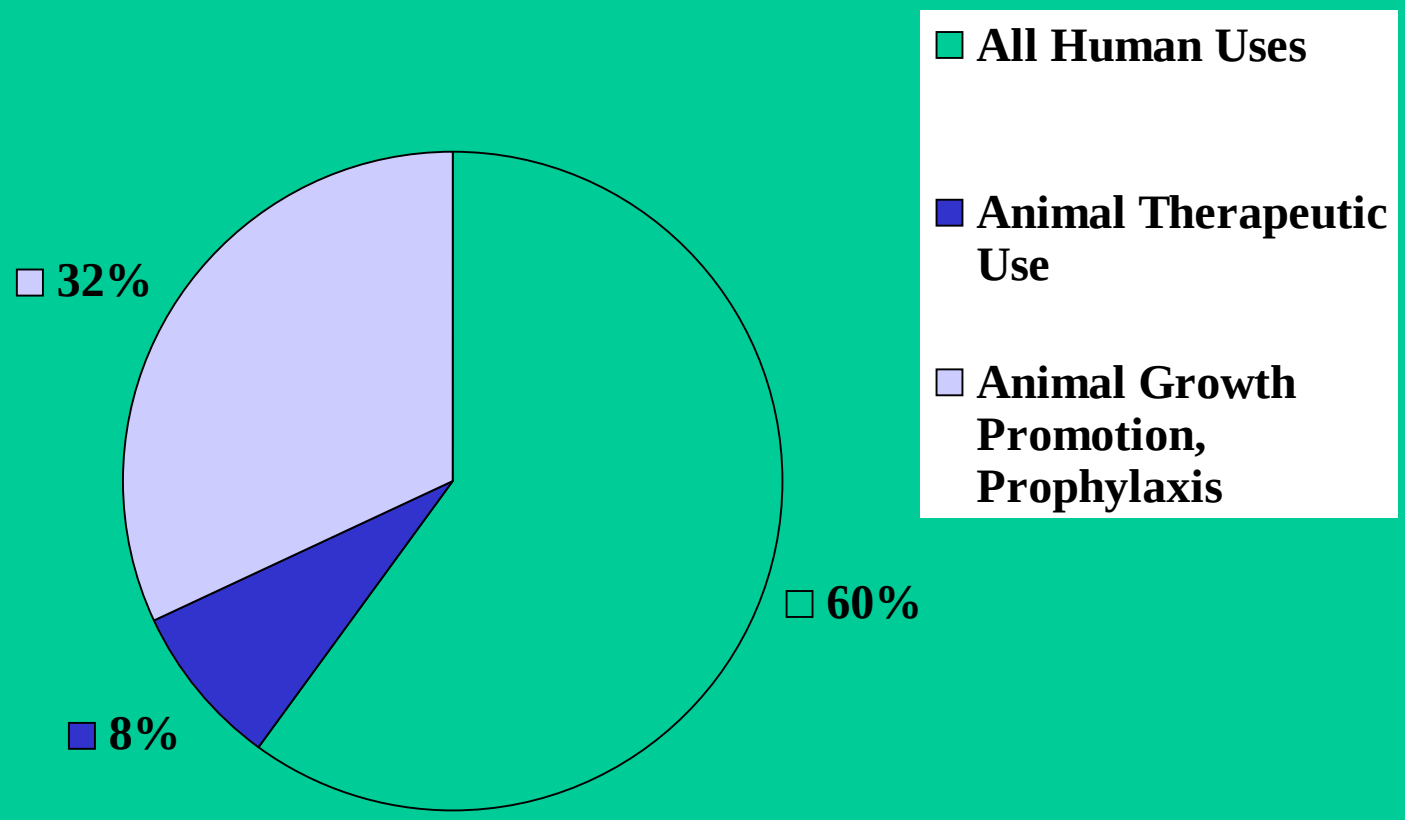
STUDY	DEF. RECENT USE	ODDS RATIO	P VALUE
Jackson (1984)	Within 1 month	**9.3**	**0.009**
Pollares (1987)	Beta-lactam within 3 mos	**9.3**	**<0.001**
Ford (1991)	Amox/Clav within 3 mos	**6.8**	**0.009**
Tan (1993)	Beta-lactam within 3 mos	**3.7**	**0.008**
Nava (1994)	Beta-lactam within 3 mos	**3.5**	**<0.001**
Moreno (1995)	Beta-lactam within 3 mos	**3.6**	**<0.001**
Block (1995)	Within 7 days	**6.7**	**<0.001**

Dowell, Am Fam Physician (1997) 55:1647

The Problem with Resistance

- Increased Morbidity/Mortality
- Increased Incidence of Disease
- Increased Duration of Illness
- Increased Cost of Treatment

Institute of Medicine Estimates

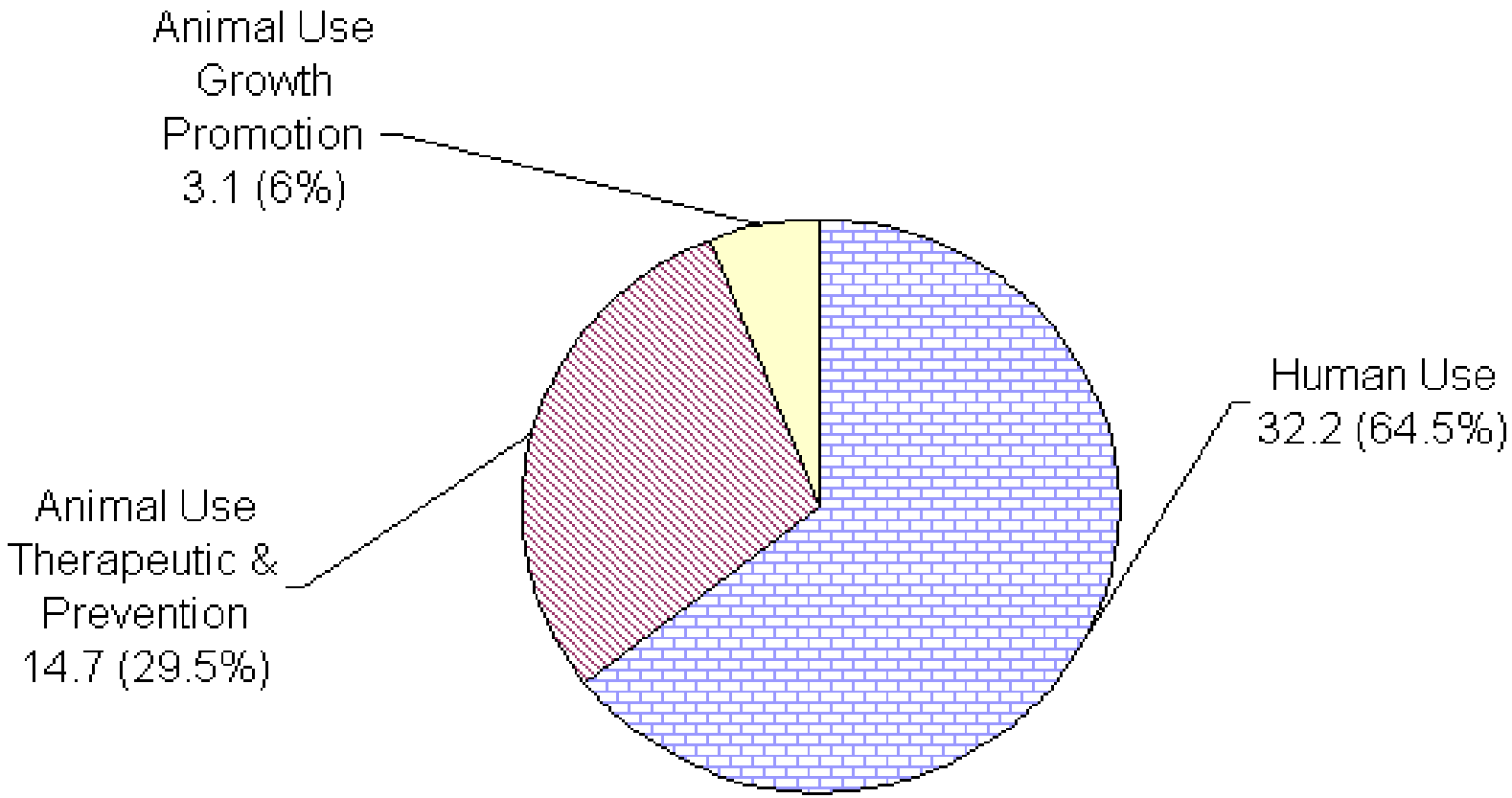


Total Annual Use: 50,000,000 Pounds

Antimicrobial Resistance: Issues and Options. Forum on Emerging Infections. Institute of Medicine , 1998.

Percentage of Antibiotics Used in the United States in 1998*

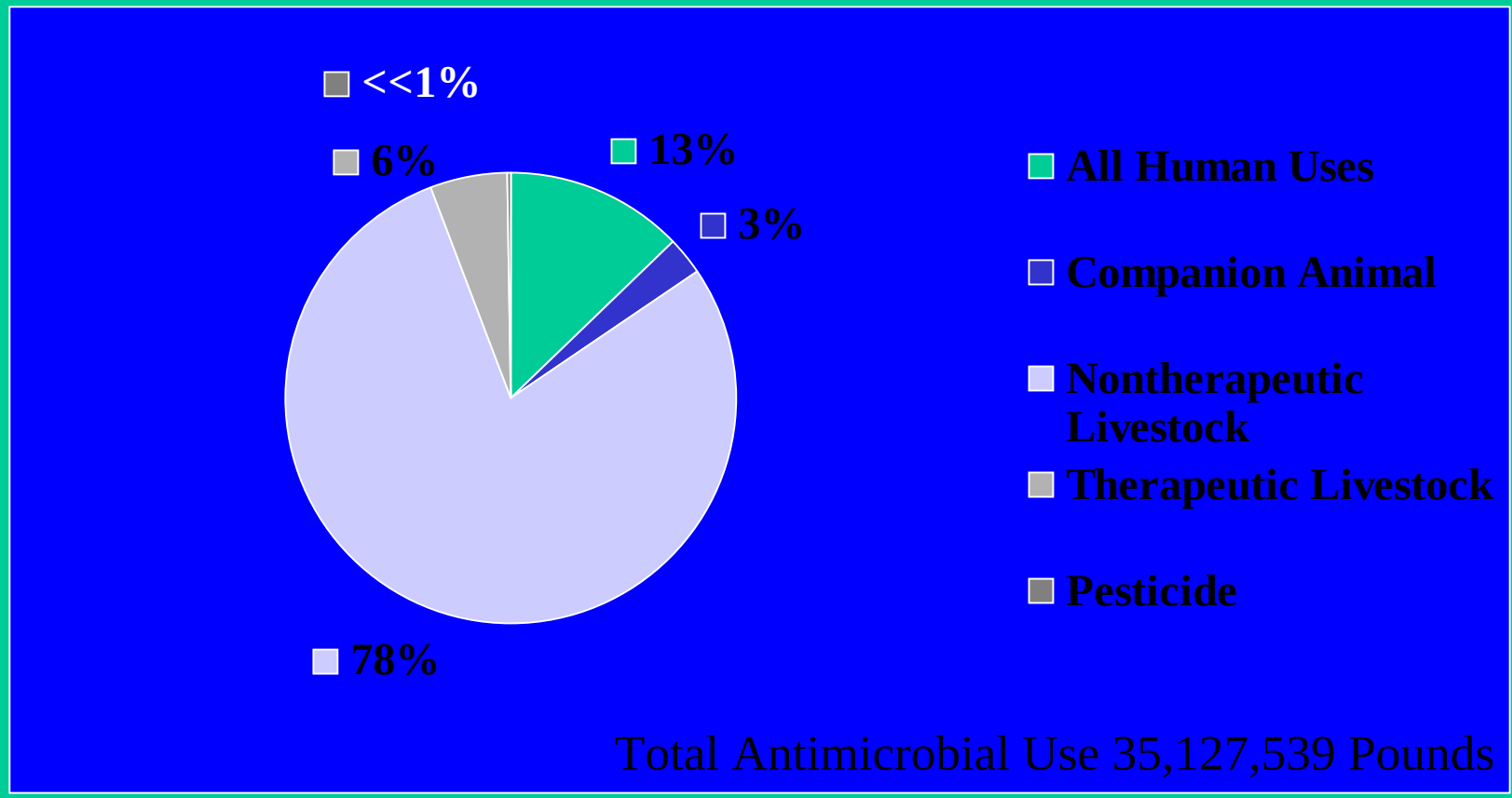
Figures Reported in Millions of Pounds and Percentages



http://www.ahi.org "Industry Perspective on Antibiotic Resistance Concerns in Food Producing Animals." R Carnevale, AHI, October, 2000.

USC Estimate of Antimicrobial Use

(Hogging It! Estimates of Antimicrobial Abuse in Livestock. USC, 2001)



WE DON'T KNOW

who is using how much of which drug for what!

Millions of Pounds of Antibiotics
are used annually in healthy animals.

Antimicrobial Resistance: Issues and Options. Forum on Emerging Infections. Institute of Medicine , 1998.
Hogging It! Estimates of Antimicrobial Abuse in Livestock. UCS, 2001

Antimicrobials FDA Approved for Growth Promotion

Amprolium

Arsanilic acid

BACITRACIN

Bambermycin

Carbadox

CHLORTETRACYCLINE

ERYTHROMYCIN

Laidlomycin

Lasalocin

LINCOMYCIN

Monensin

OXYTETRACYCLINE

PENICILLIN

Roxarsone

Tiamulin

TYLOSIN

VIRGINIAMYCIN

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

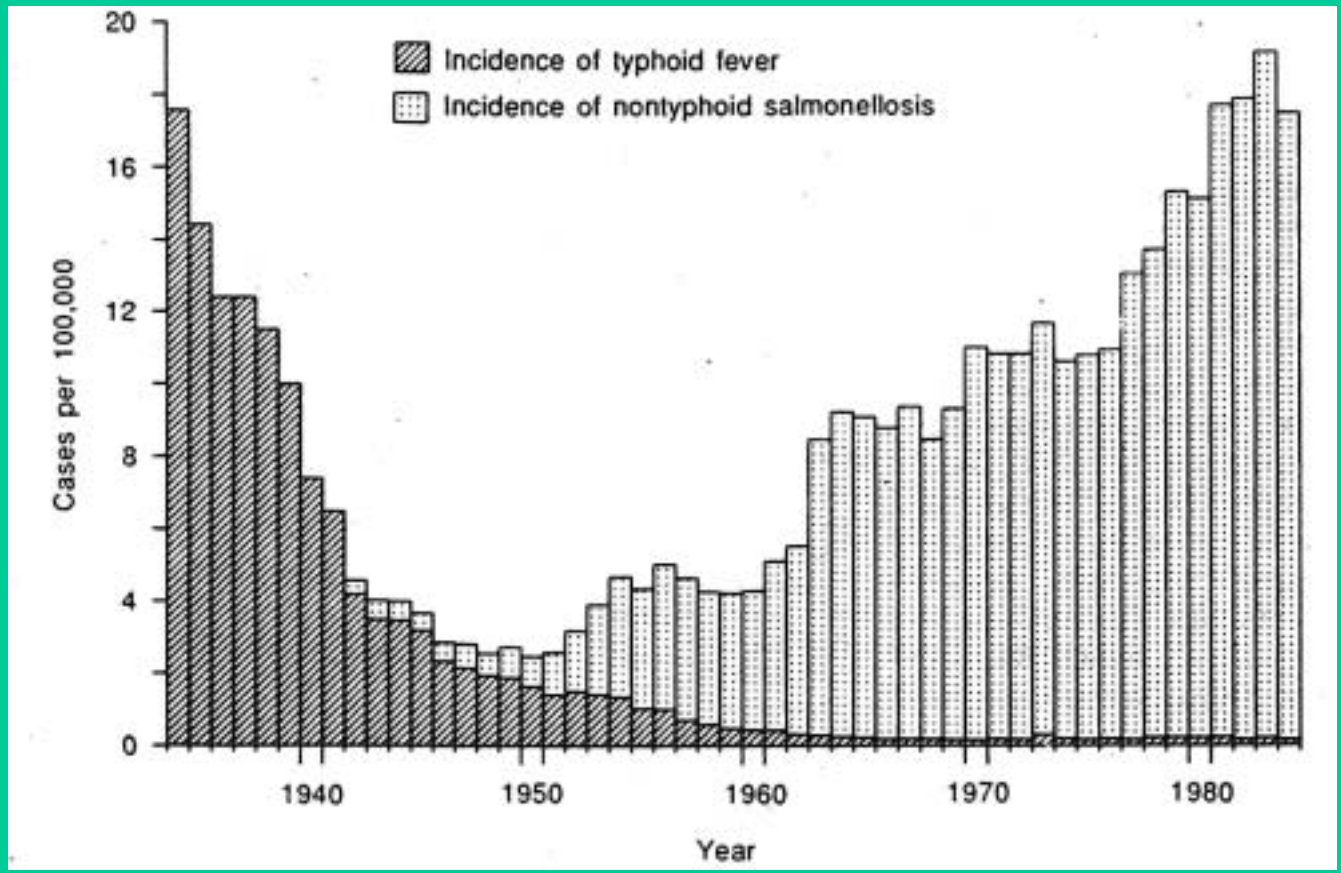
Annual Foodborne Disease in US

- 76,000,000 illnesses
- 325,000 hospitalizations
- 5,000 deaths

(30% foodborne illness is bacterial)

Mead, et al. 1999 EID Vol 5(5)

Rising Salmonella typhimurium



Cohen and Tauxe. Science (1986) 234:964

Selected Bacterial Foodborne Illnesses

Agent	***Est #***	***% FB***	***% Hosp***	***CFR***
***Campy* spp**	**2,453,926**	**80**	**10**	**0.1**
Salmonella (*nontyphoida*l)	**1,412,498**	**95**	**22**	**0.8**
***Listeria* sp**	**2,518**	**99**	**92**	**20.0**

Mead, et al. 1999 EID Vol 5(5)

Antibiotics in Feed Select Resistant Flora

- 325 chickens, ± tet-feed
- 2 weeks
  - >90% chickens excreting 100% resistant coliforms
- 12 weeks
  - 2/3 chickens resistant to more than one drug class
  - ¼ resistant to 4 classes
- Spread–humans & controls

Levy, NEJM (1976) 295

Animal ⟷ Animal

- Proximity--crowding
- Stress reaction
  increases bacterial shedding
- Purchase, sale and
  transportation of animals

- Exposure to antibiotics

Levy and Miller, 1989. P 390

Changes in Agriculture Promoting Dissemination

- Increases in Factory Farms
- Concentrated, high volume slaughter
- Broad food distribution

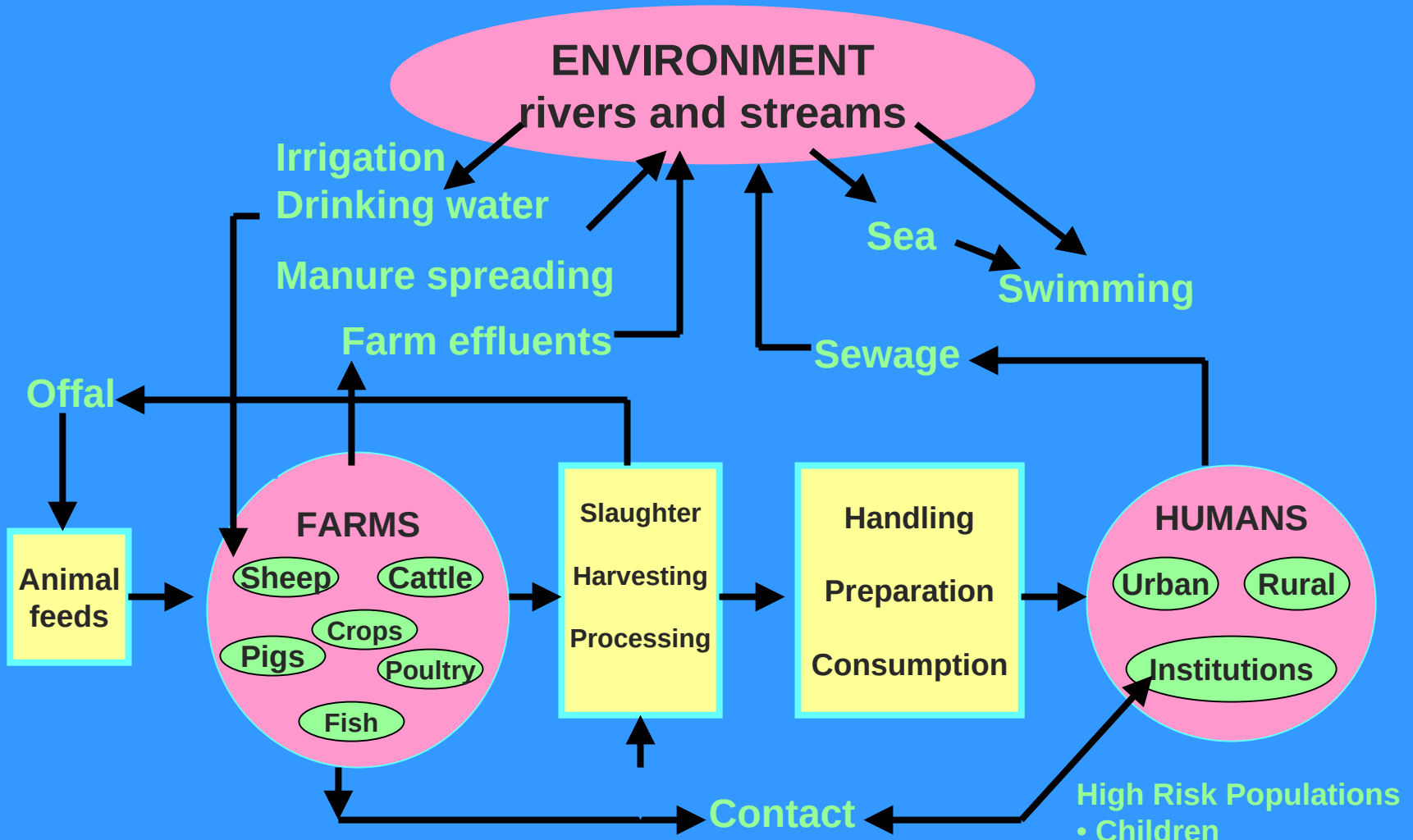
Growth Promoters -- Human Pathogens

Animal → Food → Human

- Pathogen: MDR plasmid typed Salmonella outbreak
  - People who consumed beef traced to feedlot
  - Nosocomial spread with one death
  - Illness at adjacent dairy farm in animals, farm families and extended families
- Feedlot – non therapeutic chlortetracycline

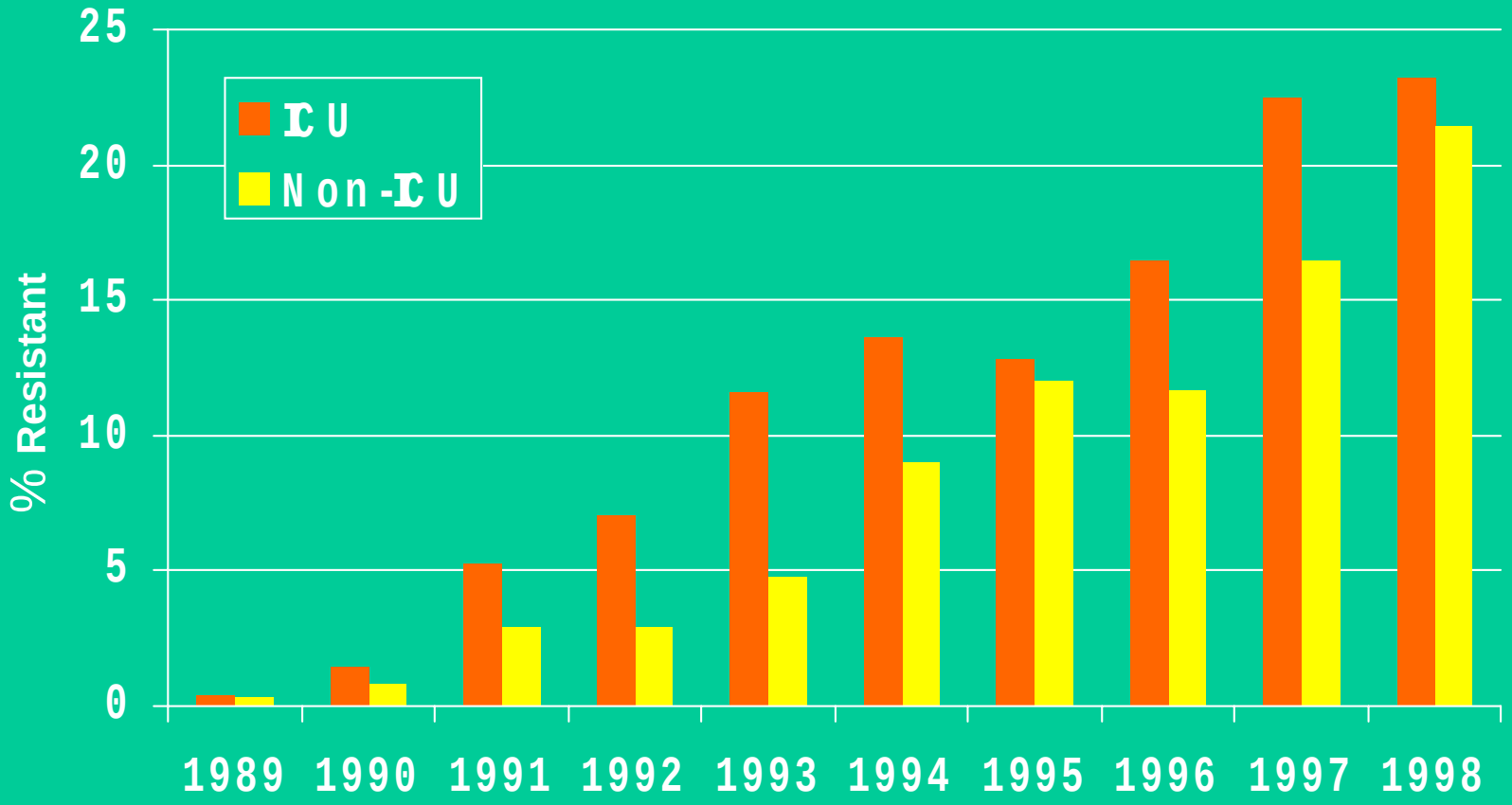
Holmberg, NEJM (1984) 311:617-22

Many Routes of Exposure/Transfer



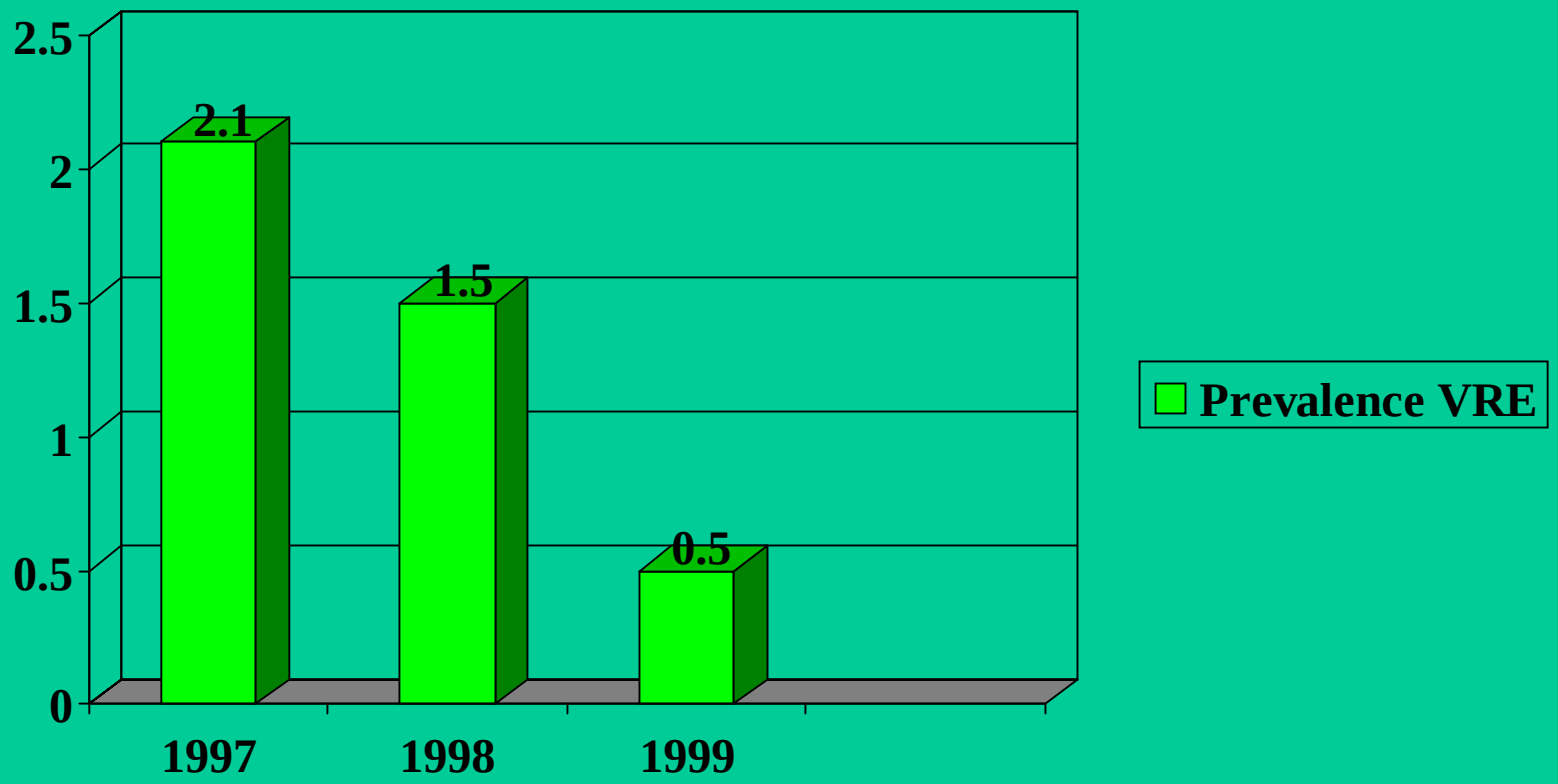
Adapted from NcNab et al. 1996,
Courtesy of Dr. Ruth Etzel

*Emerging Vancomycin-resistant Enterococcal Infections**

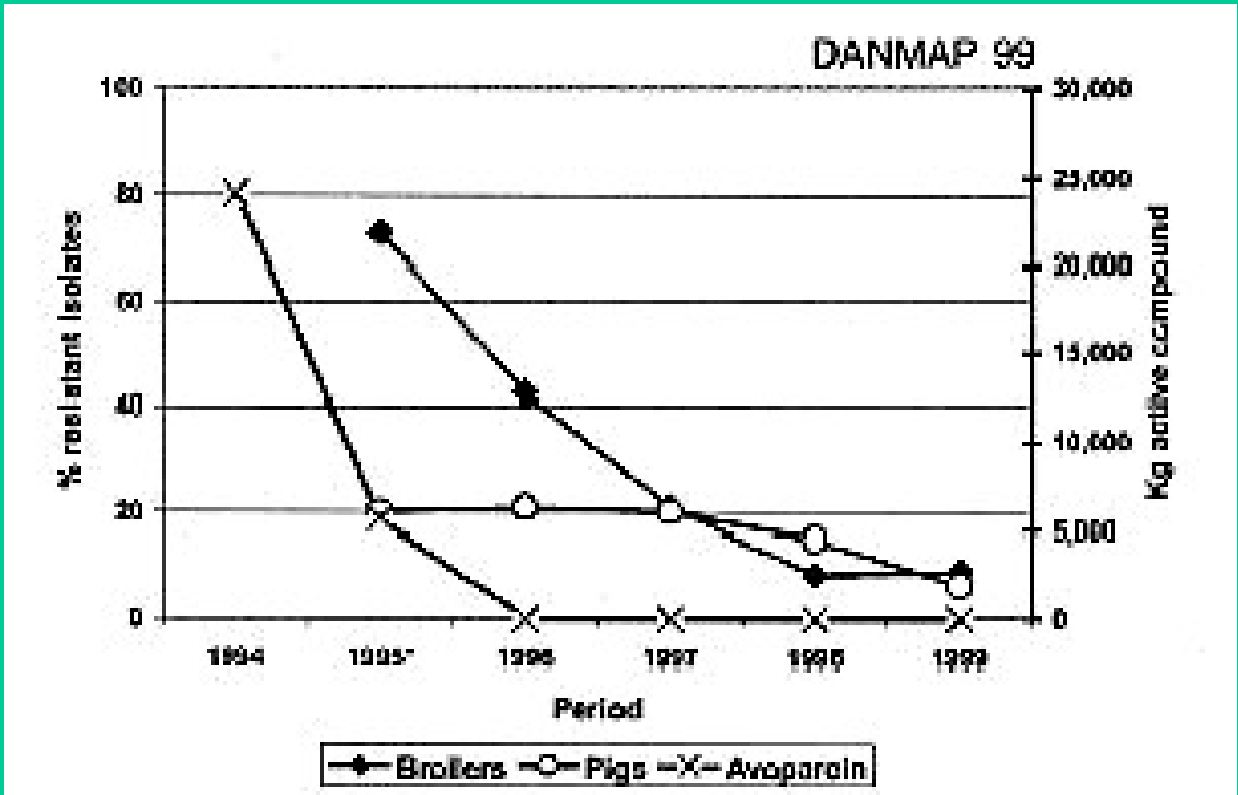


* in U.S. NNIS Hospitals

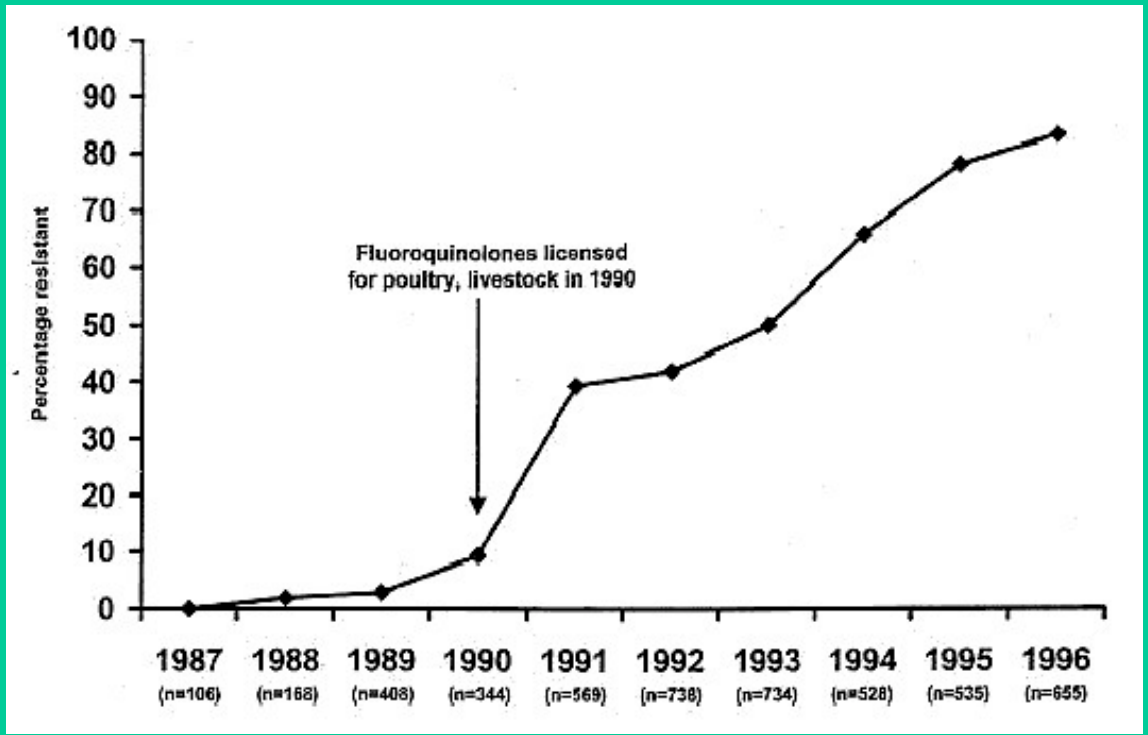
Siouxland Reversal Story



Good News: Reversibility

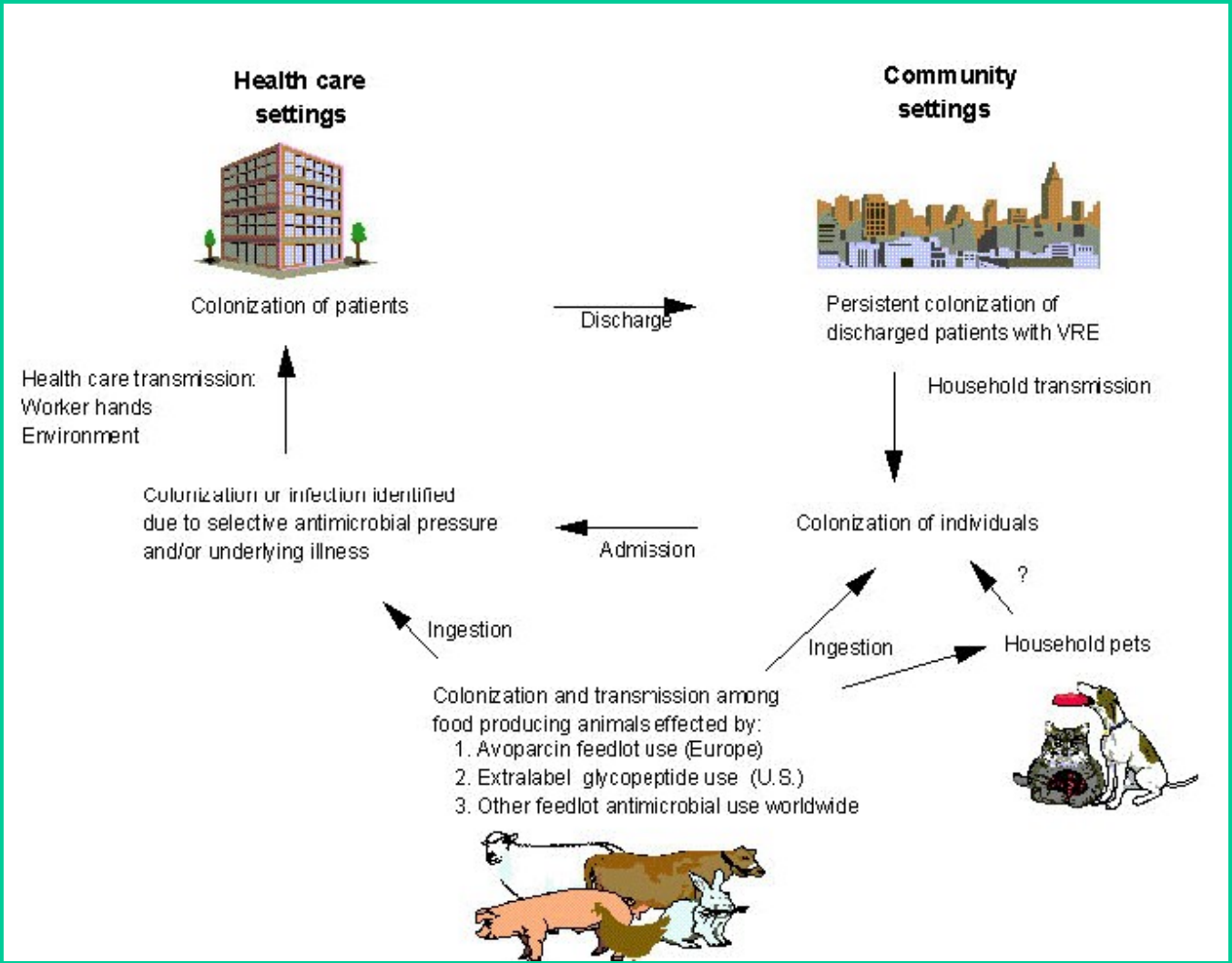


Quinolone-resistance in Human Isolates of C. jejuni/coli in Spain



Smith in CAMPYLOBACTER
ASM Press, 2000

Interconnected Ecosystems



http://www.cdc.gov/ncidod/eid/vol3no3/mcdonald.htm

Recommendations: An Interdisciplinary Approach

- Universal judicious use
- Infection control, human & animal settings
- Restrict critical use antibiotics
- Aggressive Surveillance of Resistance
- Gather Accurate Data on Antibiotic Use
- R & D, new drug, vaccine, prebiotic, probiotic
- Education
- Advocacy

Interdisciplinary Team Members

- Physicians
- Veterinarians
- Public Health Practitioners
- Farmers and Farm Corporations
- Scientists
- Pharmaceutical Companies
- Politicians
- Regulators
- Advocates
- Citizens

"The rise in frequency of resistant organisms in our environment is the obvious result of antibiotic usage. The only means to curtail this trend is to control the indiscriminate use of these drugs. All areas of antibiotic usage deserve critical evaluation."

Stuart Levy, NEJM, 1976

Suggested WebSites

- www.cdc.gov/drugresistance/index.htm
- http://www.fda.gov/cvm/
- http://www.who.int/emc/amr.html
- www.apua.org
- www.environmentaldefense.org
- www.iatp.org
- www.ucsus.org